TOBACCO ALLERGY IN PATIENTS WITH BRONCHIAL ASTHMA

by

I. Stahle and L. Tibbling

In 21 per cent of 233 patients with exogenous asthma bronchiale asthma attacks were triggered by inhalation of tobacco extract. A positive intracutaneous test with tobacco extract was far more common ($p < 10^{-6}$) in patients with a positive than those with a negative response to provocation by tobacco extract. After three years of hyposensitization 84 per cent showed a negative response to provocation. The conclusion is that tobacco smoke may trigger asthma by means of an allergic reaction. Exposure to tobacco smoke must be investigated on the basis of case reports of asthmatics. Asthmatics who are hypersensitive to tobacco smoke should be afforded a smoke-free work and leisure environment.

Bronchial asthma is a diagnosis based on the symptomatology. From the standpoint of treatment and prognosis, the disease is usually classified into an exogenous and an endogenous form, between which, however, one finds floating transitions.

The exogenous form is triggered by a specific allergen and is most common among children and youth.

The endogenous form, in which specific antigens cannot be demonstrated as the triggering factor, is primarily seen in persons over 35 years old. Patients with this form of asthma often display the picture of a chronic bronchitis between attacks, and their asthma complaints are exacerbated during periods of infection. In a study of the effect of tobacco smoke on asthmatics, it is therefore reasonable to assume that endogenous asthma is exacerbated if the patient is an active smoker, since tobacco smoking gives

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TOBACCO ALLERGY IN PATIENTS WITH BRONCHIAL ASTHMA
[Tobaksallergi hos patienter med asthma bronchiale]

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rise to a chronic bronchitis. For both the smoking and the nonsmoking asthmatics, however, it is of interest to know whether tobacco smoke, besides its nonspecific bronchitis stimulating effect, can give rise to asthma attacks on the basis of tobacco allergy.

Purpose

The purpose of this study was to investigate in a retrospective records study the incidence of asthma attacks after inhalation provocation with tobacco extract in patients with bronchial asthma and to put the results of the provocation tests into a relationship with the intracutaneous tests, smoking consumption, anamnestic complaints regarding tobacco smoke, and sensitivity to other antigenic substances. The intent was also to investigate retrospectively whether a three-year hyposensitization therapy with tobacco extract in nonsmokers would cause any change in provocation tests that were positive before the treatment.

Material and Methods

The retrospective study encompasses all patients who were referred during 1971 to the Kolmarden Hospital for an asthma examination and who, either after an intracutaneous test displayed positive reactions to some specific allergen, or who had a history which gave rise to suspicion of hypersensitivity to some specific substance. No pure cases of endogenous asthma were included.

The material included 125 men and 108 women, totalling 233. The age distribution and the average time for which the patients had had asthma at the time of examination are shown in Fig. 1.

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In the study on the effect of hyposensitization with tobacco extracts, a sample was included which had been treated during the years 1969-71. It consisted of 31 patients (16 men and 15 women), all nonsmokers with positive provocation tests with tobacco extracts, with a history of tobacco hypersensitivity, and considered to be in need of a hyposensitization therapy. During a period of three years, these patients received monthly subcutaneous injections of a maximum of 1 ml of tobacco extract. After the hyposensitization therapy, provocation tests were conducted once more but no intracutaneous tests were performed except in a few isolated cases.

The tobacco extract used was manufactured by Vitrum upon special order by the Kolmarden Hospital. The extract was made from American tobacco by suspending the tobacco in a physiologic saline solution, i.e., by the same operating principle as used to make other allergens. This tobacco extract differs from the other Vitrum solutions used in this country for tobacco tests, the latter being made by allowing tobacco smoke to bubble through a saline solution.

For the intracutaneous test with tobacco extract, 0.1 ml of the extract diluted to 1 to 100 was used. A positive intracutaneous test was considered to be present with a spot size of more than 20 mm diameter. For the inhalation provocation, tobacco extract was used in a dilution of 1:10. If, after two inhalations, no bronchoconstriction occurred, the inhalation was repeated 5 minutes later with three inhalations and 15 minutes later with five inhalations. The provocation test was evaluated as positive if, following the test, sibilant rhonchi could be auscultated over both lung fields or if the average of three peak flow measurements declined by more

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than 20% compared with measurements before the provocation. Suspicion of tobacco hypersensitivity was considered present if the patient, when giving his history, reported suffering aggravation of his asthma complaints upon his exposure to tobacco smoke. Such suspicion is called a "history of tobacco hypersensitivity" in the following.

The allergen extracts from dust, mold, pollen, animal epithelium, and food substances were all standard Vitrum solutions. At the time when the study was performed, neither RAST or PRIST was available.

Fischer's exact test was used for the statistical processing.

Results

Skin Test with Tobacco Extracts

Of 233 asthma patients, 39 displayed a positive intracutaneous test (Table I). Of these, 21 were found among the 48 provocation-positive patients and 18 among the other 189 in the study sample. The frequency of positive skin tests among the provocation positives (42%) differs highly significantly from the frequency of positive skin tests among the provocation negatives (10%): $p < 10^{-6}$.

Provocation with Tobacco Extracts

Out of 233 patients, 48 had a positive provocation test with tobacco extract, i.e., 21% (see Fig. 1 and Table I). No difference existed between the sexes. The tobacco hypersensitivity was proportionally somewhat more common among the older patients. In ten of the 48 cases that were positive to tobacco extracts provocation, the tobacco extract was the only one of all the allergen extracts tested which induced asthma attacks, constituting almost 4% of the entire sample.

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Anamnestic Tobacco Hypersensitivity

In 79% (39/48) of the provocation-positive patients, the history indicated hypersensitivity to tobacco smoke. The corresponding figures for the provocation negatives were 11% (21/185), which differs significantly ($p < 10^{-19}$) from the provocation positive.

Smoking Habits

In the provocation-negative group of 185 patients, 38% of the men and 35% of the women were smokers, figures which do not differ from the national average. In the provocation-positive group, 27% (13/48) were smokers.

Table 1. Outcome of intracutaneous test and inhalation provocation with different allergen extracts in 233 patients with bronchial asthma. Figures are given in per cent

	To-bacco	Dust	Mold	Pollen	Animal epithe-lium	Food sub-stances
125 men:						
Positive intracutaneous test	15	20	5	54	51	40
Positive provocation test	24	9	3	46	21	14
108 women:						
Positive intracutaneous test	24	28	14	67	44	58
Positive provocation test	24	23	8	46	31	23

Other Allergens

The result of the intracutaneous test and provocation with extracts from tobacco, dust, mold, pollen, animal epithelium, and food substances is shown in Table I. Almost half were pollen allergics (121/233), every fifth an animal allergic (52/233), and/or tobacco allergic (48/233) and every seventh one was allergic to dust (32/233).

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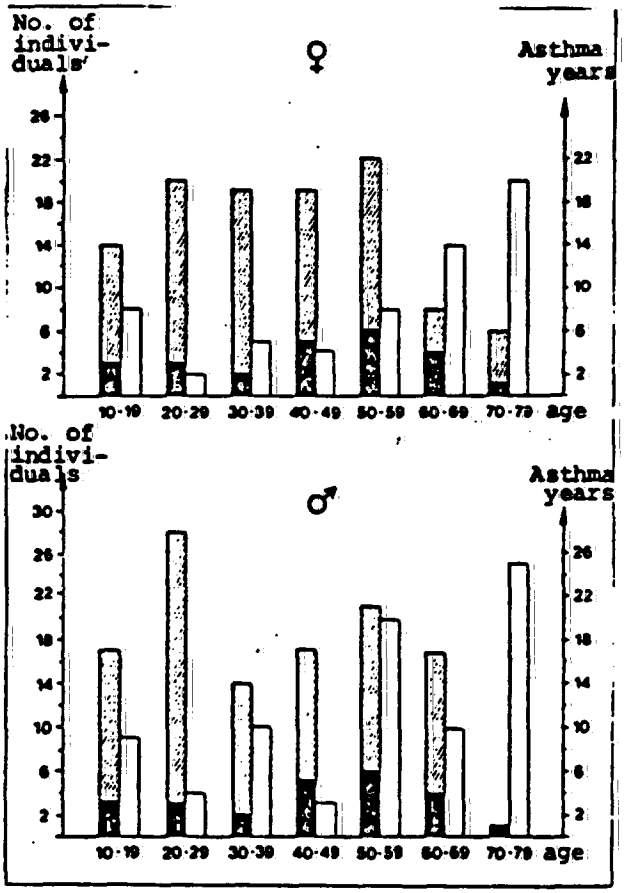

Fig. 1. Age distribution of 125 men and 108 women with bronchial asthma. The left-half of the column indicates the number of individuals within an age group, the black columns the number of cases displaying positive provocation test with tobacco extracts. The right blank half of the columns indicates the number of years for which the respective age groups had bronchial asthma on the average (asthma years).

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The greatest discrepancy between positive intracutaneous test and provocation test was present for the food substance extract.

Hyposensitization Therapy with Tobacco Extracts

Of the 31 nonsmokers with positive provocation tests from tobacco extracts and who were sensitized during a three-year period, 13 (42%) had a positive intracutaneous test before the treatment. The provocation test with tobacco extract after the treatment period had ended was negative in 26 cases (84%).

In only five cases of the 13 skin positive cases before treatment, were new intracutaneous tests performed after the treatment. Four of them had negative results.

Discussion

Reactions of the airways during exposure to tobacco smoke have been the subject of numerous studies. Speer (1968) studied the subjectively reported complaints of 191 allergic and 250 nonallergic nonsmokers when they were exposed to tobacco smoke. Coughing was reported in 46% by allergics and in 25% of nonallergics, sneezing in 23 and 4% respectively, eye irritation in 67 and 29% respectively.

O'Connell and Logan (1974) studied the role of exposure to tobacco smoke in 400 asthmatic and 228 nonasthmatic children. If any of the parents smoked, the complaints of the asthmatic child were aggravated in 67% by exposure to smoke as opposed to 26% if neither parents smoked. This difference could be explained by the fact that the asthmatic children exposed to tobacco smoke daily have been sensitized to tobacco smoke. Zussman (1970) published the results of a hyposensitization therapy of 16

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atopic persons, most of them with hayfever, who were clinically tobacco allergic. In ten of these, the symptoms decreased by more than 75%. In the remaining six cases, the symptoms were cut in half after the hyposensitization treatment. These results speak in favor of an allergen in tobacco smoke.

In 1976, Becker et al. isolated a glucoprotein with antigenic properties from both tobacco extract and tobacco smoke condensate, to which almost one-third of the smokers and nonsmokers reacted positively in intracutaneous tests.

Tobacco Allergy?

In this study, provocation with tobacco extract was used for the first time against the "shock organ", at which time every fifth asthmatic reacted with attacks of asthma. The highly significant difference in the frequency of positive skin tests between provocation-positive and provocation-negative asthmatics testifies that the tobacco smoke transports potentially allergenic substances.

The fact that 84% of the provocation-positive nonsmokers were provocation negative after hyposensitization further strengthens this belief. Possibly also speaking in favor of this is the observation that 73% of the provocation-positive patients were nonsmokers and therefore should have been sensitized through passive smoking. This latter agrees well with O'Connell's and Logan's (1974) finding that children with asthma who were exposed to tobacco smoke suffer more complaints if they come from smoking than if they come from smoke-free home environments.

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Tobacco Smoke Versus Tobacco Extract

The fact that one-third of the asthmatics who reported anamnestic aggravation of their asthma complaints in smoke-polluted environments did not have a positive provocation test may have many causes. The composition of the tobacco smoke and the tobacco extract are different in part. Many of the gases that are formed upon condensation or combustion during smoking have a nonspecific bronchus-irritating effect and are not found in the tobacco extract. Thus, for instance, the high content of nitrous gases in tobacco smoke may be suspected of triggering asthma attacks.

It is therefore possible that asthma attacks are more common among patients who are exposed to tobacco smoke than is indicated in this study with tobacco extract where several nonspecifically acting gases were eliminated? Of course, this does not exclude the possibility that the tobacco extract may, in part, have been able to trigger nonspecific asthmatic reactions in those who remained provocation positive. One possibility of solving this riddle will be obtained when the RAST test is available with reliable tobacco extracts.

Trigger Mechanism

Except for an antigen-antibody reaction and nonspecific reactions, an additional trigger mechanism may also be suspected of having caused the asthma complaints in passive and active smokers, i.e., infection. Cameron et al. (1969) observed that acute upper respiratory infections were more common among children from homes with parents who smoked than among children with nonsmoking parents. Harlap and Davies (1974) studied the incidence of bronchitis and pneumonia in 10,000 newborn children in

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relationship to cigarette consumption of the mother. The more the mother smoked, the greater the risk the newborn child ran of contracting a respiratory infection. Finklea et al. (1971) found that the antibody titers after a sustained infection were significantly lower in smokers than in nonsmokers.

The fact that in this study, 84% of the tobacco extract provocation-positive patients became provocation negative after hyposensitization therapy could perhaps be ascribed in part to a reduced infection susceptibility with a smaller tendency to react to any possible nonspecific irritation. An infection mechanism, however, could not explain the highly significant differences in the intracutaneous tests between provocation-positive and provocation-negative patients. It is also improbable that if nonspecific reactions consequent to bronchitis underlay a positive provocation test, the latter would have been influenced at such a high frequency by the general treatment during the three-year period when the hyposensitization therapy was underway, since the majority of the patients had been treated for their bronchial asthma for at least six years before the tests had begun.

The tobacco-promoting asthma attacks in smokers showed the tendency of smokers to continue tobacco smoking despite somatic complications, which is an illustration of the strength of the nicotine dependence (Martelius, Tibbling 1977).

In some cases, presumably, the patient is unaware of the relationship between his asthma and smoke consumption (Blue 1970).

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Behind the cause of the asthma attacks in both the active and the passive smoker, one probably finds not only allergic but nonspecific and infectious mechanisms. For the patient, the underlying cause should be of no interest unless a hyposensitization treatment is available to him. However, it appears appropriate in conformance with other allergy treatments, to eliminate, above all, the agent which gives rise to the complaint, i.e., tobacco smoke. For this, however, it will be necessary for the examining doctor to be aware that tobacco smoke can cause asthma attacks in at least every fifth asthmatic and that the majority of them are nonsmokers.

In those cases when smokers in the environment of the asthmatic cannot be persuaded to abstain from tobacco smoking, something which is unquestionably difficult, a hyposensitization treatment may be a conceivable alternative.

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